BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/707,900	11/08/2000	Moon Jong Noh	54751-015	9053

7590 01/24/2002

Attn: Joseph H. Kim, PhD
SQUIRE, SANDERS & DEMPSEY L.L.P.
14th Floor
801 S. Figueroa St.
Los Angeles, CA 90017-5554

EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 01/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/707,900	Applicant(s) NOH ET AL.	
	Examiner Michael Wilson	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-22 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-22 is/are rejected.

7)☒ Claim(s) 9 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-22 are under consideration in the instant application.

Specification

1. The amendment filed 10-9-01, paper number 6, is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the deletion of "mesenchymal cells" from what applicant consider a "connective tissue" is new matter. It is not readily apparent that "mesenchymal cells" was inadvertently included in the definition as originally filed. An alteration in the definition of "connective tissue" alters the scope of the invention. An alteration in the scope of the invention described in the specification as originally filed is new matter.

Applicant is required to cancel the new matter in the reply to this Office action.

Claim Objections

2. Claim 9 is objected to because of the following informalities: the upper margin of the page is too high. The text of claim 9 has been obscured by hole punches. Similarly, the margin on page 11 is too high, but the claim obscured has been amended and can now be read.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for transfecting fibroblasts with DNA encoding TGF-β1 operably linked to a promoter, transplanting the transfected fibroblasts into a joint space of a mammal such that expression of TGF-β1 occurs resulting in generating hyaline cartilage, does not reasonably provide enablement for treating arthritis, using any protein of the transforming growth factor superfamily, any connective tissue cells or regenerating any connective tissue as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specific combination of vector, cell and modes of delivery required to target a desired tissue and regenerate tissue *in vivo* is unpredictable. Miller (1995, FASEB J., Vol. 9, pages 190-199) review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient

delivery systems" (page 198, column 1). Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). Crystal (1995, Science, Vol. 270, page 404-410) also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409).

More specifically, at the time of filing Naughton taught transplanting foreskin fibroblasts to a site of cartilage damage in the presence of scaffolding and regenerating cartilage, suggested transfecting the cells with a vector encoding TGF-β1 and suggested delivering the cells intraarticularly (Naughton, claim 1; col. 10, line 58; col. 4, line 65; col. 13, line 60 - col. 16, line 33; col. 2, line 56 and col. 18, lines 8-42 which discusses administering the cells to joints that

have damaged cartilage). Ikeda taught administering a vector encoding TGF-β1 intraarticularly to obtain TGF-β1 expression (pg 1667, col. 1, 3rd para.; pg 1669, col. 2). van Beuningen taught TGF-β1 administered intraarticularly generates articular cartilage (pg 307, col. 1, "intraarticular injections"; pg 308, col. 1, "stimulation of articular cartilage"). The art did not teach how to use fibroblasts or TGF-β1 to regenerate ligaments or tendons. The art did not teach how to use osteoblasts or chondrocytes to regenerate cartilage or any other connective tissue.

The specification does not enable using the instant invention to treat arthritis (claim 1). Arthritis in humans causes a diverse T-cell population response against not just collagen or one antigen, but a large number of undefined antigens in the arthritic joint (Fox et al., July 1995, Am. J. Med., Vol. 99, pgs 82-88; pg 87, col. 1, para. 1; pg 84, col. 4, para. 1). The specification demonstrates the invention in rabbits having cartilage defects made with a knife (pg 29, line 7). These rabbits are not an art accepted model for arthritis; nor do the rabbits correlate to arthritis. While arthritic joints require cartilage regeneration, removing cartilage reflect with a knife does not reflect the complex immune response in an arthritic joint. The specification does not teach how damaging cartilage with a knife reflects the diverse T-cell response against the undefined antigens in the arthritic joint as taught by Fox et al. The specification does not provide adequate guidance to regenerate cartilage in an arthritic joint because the cells administered may be attacked by the immune system and may not target the damaged area of cartilage.

The specification does not enable using any connective tissue transfected with DNA encoding any transforming growth factor superfamily protein to regenerate any connective tissue

as broadly claimed. Specifically, the specification does not correlate the results obtained using TGF-β1 to TGF-β2, TGF-β3, BMP-2, -3, -4, -5, -6 or -7 such that cartilage would be regenerated. Nor does the specification correlate the function of TGF-β1 to TGF-β2, TGF-β3, BMP-2, -3, -4, -5, -6 or -7 such that cartilage could be regenerated. While the specification suggests using various members of the transforming growth factor family (page 13, line 26 through page 14, line 9) which may share structural similarities with TGF-β1, the activities and functions of the various proteins vary. The specification does not provide the structural features or functional activity of any transforming growth factor superfamily protein required to regenerate cartilage or any other connective tissue. The specification does not teach the combination of cell, DNA and mode of delivery required to regenerate ligaments or tendons (claim 8). The specification does not teach the combination of DNA and mode of delivery to use with osteoblasts or chondrocytes such that hyaline cartilage is regenerated (claim 17) or any other connective tissue is regenerated (claim 6).

Given the unpredictability in the art taken with the guidance provided in the specification, it would have required one of skill undue experimentation to determine the specific combination of connective tissue cell, DNA and mode of delivery require to target the desired tissue and regenerate hyaline cartilage or any desired connective tissue as broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 is indefinite because it is unclear if "said connective tissue" refers to the cultured connective tissue cells or the connective tissue regenerated in claim 1. Deletion of "a" in claim 8 is also suggested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 16-21 are rejected under 35 U.S.C. 102(b) as anticipated by Agrawal (Agrawal et al., 1995, Indian J. Exp. Biol., Vol. 33, pages 708-709).

Agrawal taught transfecting NIH3T3 cells with a vector encoding TGF-β1 (page 708, column 2, last paragraph). NIH3T3 is a fibroblast cell line. Therefore, Agrawal anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claim 16-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Agrawal (Agrawal et al., 1995, Indian J. Exp. Biol., Vol. 33, pages 708-709).

Agrawal taught transfecting NIH3T3 cells with a vector encoding TGF-β1 (page 708, column 2, last paragraph). Agrawal did not teach the vector was named pmTβ1. However, at the time of filing, the nomenclature of a vector was a non-effective variable routinely utilized by those of ordinary skill in the art. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to name the vector taught by Agrawal pmTβ1. One of ordinary skill in the art at the time the invention was made would have been motivated to name the vector pmTβ1 to indicate the vector encoded TGF-β1. Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

7. Claims 1-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Naughton (Naughton et al., US Patent 5,842,477, Dec. 1, 1998) in view of Ikeda (Ikeda et al., Sept. 1998, J. Rheumatol., Vol. 25, pages 1666-1673) and van Beuningen (van Beuningen et al., Sept. 1998, Osteoarthritis and Cartilage, Vol. 6, pages 306-317).

Naughton taught transplanting foreskin fibroblasts to a site of cartilage damage in the presence of scaffolding and regenerating cartilage (claim 1; col. 10, line 58; col. 4, line 65). Naughton did not expressly teach transfecting the cells or administering the cells intraarticularly. However, Naughton suggested transfecting cells for transplant with a vector encoding TGF-β1 (column 13, line 60 - column 16, line 33) and delivering the cells intraarticularly (col. 2, line 56 and col. 18, lines 8-42 which discusses administering the cells to joints that have damaged cartilage). In addition, Ikeda taught administering a vector encoding TGF-β1 intraarticularly to obtain TGF-β1 expression (page 1667, column 1, 3rd paragraph; page 1669, column 2) and van Beuningen taught TGF-β1 administered intraarticularly generates articular cartilage (page 307, column 1, "intraarticular injections"; page 308, column 1, "stimulation of articular cartilage").

Thus, it would have been obvious to one of ordinary skill at the time the invention was made to make a vector encoding TGF-β1, transfect foreskin fibroblasts and administer the cells to the joint of animal with cartilage damage such that cartilage repair is obtained. It is noted that the claims as written encompass administering cells in the presence of scaffolding. One of ordinary skill would have been motivated to deliver the fibroblasts intraarticularly to put the cells in contact with the joint as taught by Naughton. One of ordinary skill would have been motivated to transfect the fibroblasts with a vector encoding TGF-β1 to generate cartilage as taught by Ikeda and van Beuningen. Hyaline cartilage (claim 9) is the cartilage repaired by Naughton and the articular cartilage repaired by van Beuningen because hyaline cartilage is part of articular cartilage found in articular joints (column 1, line 43; see also Naughton who taught

cartilage includes hyaline cartilage, col. 6, line 31). One of ordinary skill would have been motivated to freeze the cells using any of the methods of freezing that were well known in the art at the time of filing to prevent having to make the cells again (claim 4). The nomenclature of a vector is a non-effective variable routinely utilized by those of skill in the art; therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to name a vector taught by Naughton pmTβ1 (claims 15 and 22).

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

8. Claims 1-22 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-22 of copending Application No. 09/702718. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be

required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. MPEP § 822.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-2982.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER